

REMARKS

Reconsideration is respectfully requested in view of the following remarks and arguments.

The claims presently pending before the Examiner are 24 – 33, inclusive.

Claim Rejections – 35 USC §112

In the outstanding Office Action, the Examiner has alleged that the ratio in Claim 24(d) is indefinite. This rejection is traversed.

The Applicants understand that the Examiner is, indeed, referring to Claim 24(e). In this regard, it is clear that the cited ratio is between the PLGA coming from step d) and PLGA as such, i.e. untreated PLGA.

This is apparent also from the detailed description in WO 2005/000277 (p. 3, lines 26-27), wherein it is stated that “while in stage e), the weight ratio of PLGA originating from stage d)/PLGA as such is preferably between 16:84 and 40:60.” The fact that “PLGA as such” means “untreated PLGA” is further confirmed by all of the working Examples, e.g. on page 5, lines 2-3, wherein the “polymer thus obtained is mixed at -10°C with the same untreated type of polymer as such”.

Therefore, in Applicants’ opinion Claim 24(e) is not indefinite and the rejection under §112 has been overcome and should be withdrawn.

Claim Rejections – 35 USC §103

In the outstanding Office Action (“OA”), the previously presented claims 24-31 are rejected under 35 USC §103(a) as being unpatentable over US 5,520,923 (“Tjia et al.”) in view of WO 03/041685 (“Chen et al.”). This rejection is traversed.

In the Examiner’s view (page 4, OA), “Tjia et al disclose microparticle formulations which are manufactured using a lower alkyl alcohol, preferably ethanol (see Col. 2, lines 55-56). PLGA is specifically recited at col. 3, lines 29-40. Particle diameters are listed at col. 3, lines 41-51 and include 250 um. Heating of the solvent and particles is

done at a temperature of 45 to 60 C (see col. 5, lines 3-23). The product is then cooled to 4 C (see column 2, lines 24-27, reading on claim 1 of the instant invention). Steps e)—g) are not required steps.”

Firstly, it should be noted that only step e) is optional, since steps f) and g) are nowhere referred to as optional. Thus, steps f) and g) are required steps in the claimed process.

Secondly, Tija et al. indeed relate to (col. 2, line 66, to col. 4, line 13) “processes of preparing fused sponges of porous particulate polymer which fused sponges are suitable for use as a carrier for osteogenic protein. Generally, the process comprises:

- a) preparing a mixture of particles of a porous particulate polymer, a lower alkyl alcohol and a surfactant;
- b) heating the mixture of step (a) until the particles form a fused sponge;
- c) optionally continuing to heat the mixture for an additional period of time at a temperature of about 45° to 60°C;
- d) optionally cooling the mixture; and
- e) drying the mixture in the form of a fused sponge.” [emphasis added]

Therefore, Tija et al. do not disclose “microparticle formulations” since the final product is a fused sponge, whereas “porous particulate polymer” is a starting material. As a matter of fact, the aim of Tija et al. to prepare fused sponges is also confirmed by following paragraph (col. 8, lines 51-57), wherein the desired characteristics of the final sponge are discussed:

Structural Integrity: The fused sponges show a surprisingly high resistance to tensile forces and maintain their shape under high strain. Fused sponges made without any additives have the highest structural integrity. They show a relatively high degree of resistance to tension. Rectangular fused sponges have a higher resistance than cylindrical fused sponges.

Indeed, the Examiner has failed to identify in Tija et al. at a minimum the claimed steps a), b) (partially), d) to g) and the Applicants discern no other teachings in Tija et al. that can be said to read on the claimed combination of steps.

It should be also noted that, in Tija et al. process, the step c) referring to heating at a temperature of about 45° to 60°C is optional.

Notwithstanding the foregoing, the Examiner alleged that "Tija et al. only differs in that the amount of ethanol set out is higher than instantly claimed", thus, it is apparent that the Examiner only gave conclusory statements and did not provide an articulated reasoning with some rational underpinning as to why "the amount of ethanol" is the only difference.

Additionally, it should be remembered that the technical information available to the skilled person at the time the claimed invention was made, was that Tija et al., wishing to prepare sponges having sufficient spacing to allow mammalian osteoprogenitor cells to infiltrate and be positively influenced by (evidenced by an increase in osteogenic activity/bone growth rate) the osteogenic protein (col. 3, lines 47-51), cannot involve a grinding step that undesirably would mill the sponge.

Considering that the claimed process requires even three steps of grinding, i.e. step a), step d) and step g), as well as an extrusion step, it can be easily understood that Tija et al. *clearly teach away* from the claimed invention.

Furthermore, at col. 9, under the subtitle "B. Process Parameter Optimization", lines 33-46, it is clearly explained as follows:

In general, friability decreased as fusion temperature increased. However, deformation of both the PLGA particles and the fused sponge itself was more prevalent as fusion temperature increased. At a temperature of 60° C., sufficient fusion is achieved without completely melting the PLGA particles and with minimum friability. At temperatures

greater than 60° C., the PLGA particles lose their structure and overfuson occurs. All of the fused sponges made using a temperature gradient have good porosity. Those removed from the water bath immediately after it reached 60° C. also have excellent sponge shape. The fused sponges held for 5 minutes at 60° C. were noticeably more difficult to remove from the mold. Forceps had to be used to facilitate removal, resulting in deformation of the fused sponge.

This means that Tija et al. expressly teach not to exceed the temperature of 60°C, whereas conversely, in step b) of the claimed process, PLGA and ethanol in specific ratios can be heated up to 65°C.

In this regard, accordingly, *Tija et al. teach away* from the claimed invention because “a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the [Applicant].” *Tec Air Inc. vs. Denso Mfg. Michigan Inc.*, 192 F.3d 1353, 1360 (Fed Cir. 1999). See also MPEP §§2141.02 and 2145 (prior art must be considered as a whole, including any disclosure that teaches away from the claimed invention). In this case, a person of ordinary skill, upon reading Tija et al., clearly would be led in a direction divergent from the path that was taken by the Applicants.

Considering that a “teaching away” typically arises when a reference provides an explicit disclosure which “criticizes, discredits, or otherwise discourages” a claimed combination, the Examiner should keep in mind that this is absolutely the situation here, since Tija et al. explicitly and expressly teach not to exceed the temperature of 60°C, as above discussed.

It follows that it turns “improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983)” (MPEP 2145). That a reference teaches away is sufficient on its own to defeat a *prima facie* case of obviousness. See *Winner Int'l Royalty Corp. vs. Wang*, 202 F.3d 1340, 1349-50 (Fed Cir. 2000).

In fact, one of ordinary skill in the art would have never even considered combining Tija et al. with Chen et al., since Chen et al. pertain to a different field of endeavor and, in any event, does not add anything useful to the teaching of Tija et al.. As

a matter of fact, Chen et al. refer to gel compositions that contain an agent that renders the composition thixotropic to facilitate injection of the gel into a subject with minimal discomfort to the subject, wherein (p. 11, lines 16-18)

"thixotropic agent" as used herein is one that increases the thixotropy of the composition in which it is contained, promoting shear thinning and enabling use of reduced injection force.

Thus, at the time the claimed invention was made, a skilled person would have had no reason at all to combine the process of Tjia et al. (involving the preparation of sponges having a high degree of resistance to tension and defined porosity to allow mammalian osteoprogenitor cells to infiltrate) with the gel of Chen et al. (involving neither the preparation of sponges, nor porosities, but requiring a thixotropic agent to promote shear thinning and facilitate the injection), much less with any reasonable expectation of success.

Additionally, if the process of Tjia et al. was modified to form a gel composition in the direction of Chen et al., this modification would render the resulting product unsatisfactory and inoperable for their primary intended purpose of making "sponges having sufficient spacing to allow mammalian osteoprogenitor cells to infiltrate and be positively influenced by (evidenced by an increase in osteogenic activity/bone growth rate) the osteogenic protein" (see col. 3, lines 47-51), and having "high degree of resistance to tension" (see col. 8, lines 51-57); as well as the modification would change the principle of operation of Tjia et al.: this also counsels against a finding of obviousness. MPEP 2143.01

Furthermore, the Federal Circuit has explicitly stated that "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed Cir. 1991)" (MPEP 2143) [emphasis added]

It is submitted that when an Office Action fails to provide a "clear articulation of the reason(s) why the claimed invention would have been obvious", it is likely that the rejection is based upon improper hindsight reasoning. The BPAI recently stated in *Ex parte Schoemann et al.*: "it is improper to base a conclusion of obviousness upon facts

gleaned only through hindsight" and held that "absent hindsight, we see no reason, and the Examiner has not provided an adequate articulation of a reason, why a person of ordinary skill in the art would have been led to modify Stein by the teachings of I0 in the manner suggested by the Examiner." In support of the foregoing, the BPAI cited the following Federal Circuit precedent:

"To draw on hindsight knowledge of the patented invention, when the prior art does not contain or suggest that knowledge, is to use the invention as a template for its own reconstruction — an illogical and inappropriate process by which to determine patentability." *Sensorics, Inc. v. Aerasonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996) (citing *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 1553 (Fed. Cir. 1983))." (Ex Parte Schoemann et al., Appeal No. 2009-4371 (BPAI))

In view of the above, it is also reaffirmed that in the outstanding Office Action, the obviousness rejection only includes conclusory statements and does not provide an "articulated reasoning with some rational underpinning". Thus, the Office Action has failed to establish a *prima facie* case of obviousness.

The Examiner, starting from the presumption that steps e)-g) are not required steps and that "Tjia et al. only differs in that the amount of ethanol set out is higher than instantly claimed", alleged that the *missing* amount of ethanol could have been found in Chen et al., thus rendering obvious the claimed process. However, besides the argumentations given above belying this allegation, it should be reminded that the Supreme Court in *KSR v. Teleflex* stated that: "it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does."

Actually, the requested apparent reason to combine references is missing in the Office Action as a whole, since it is, indeed, quite clear that, conversely, there are many reasons against said combination.

In this regard, the Examiner had provided no reasoning or evidence to explain how the process of Tjia et al., involving only steps of mixing, heating and drying to give a sponge, in combination with the gel of Chen et al., could result in a process involving a step of extrusion and three steps of grinding, as currently claimed.

Similarly, it should be remembered that the Examiner fails to explain how a skilled person would have considered to combine the process of Tija et al. (involving the preparation of sponges having a high degree of resistance to tension and defined porosity to allow mammalian osteoprogenitor cells to infiltrate) with the gel of Chen et al. (involving neither the preparation of sponges, nor porosities, but requiring a thixotropic agent to promote shear thinning and facilitate the injection), **much less with any reasonable expectation of success.**

In summary, in view of the fact that:

- the cited references fail to teach all the limitations of the claimed invention, so that there is no apparent reason to combine the references as one would not arrive at the claimed invention (KSR, 127 S. Ct. 1727), as proven above;
- a proper rationale for combining references is missing if one reference “teaches away” from the other reference, by providing an explicit disclosure which “criticizes, discredits, or otherwise discourages a claimed combination”, as proved above;
- a proper rationale for combining references is missing if one reference is used to modify, in a combination, another reference, however the proposed modification would render the modified reference inoperable for its intended purpose (MPEP 2143.01), as proved above;
- a proper rationale for combining references is missing if one reference is used to modify, in a combination, another reference, however the proposed modification would change the principle of operation of one of the references (MPEP 2143.01), as proved above;
- the obviousness rejection only includes conclusory statements and does not provide an articulated reasoning with some rational underpinning as to why the claimed invention would have been obvious, as proved above;

it follows that the Office Action has failed to establish a *prima facie* case of obviousness.

Because the Examiner has failed to factually support a *prima facie* case of obviousness, "an applicant is under no obligation to submit evidence of nonobviousness", MPEP §2142.

For at least the above reasons, the obviousness rejection under § 103(a) has been overcome and it is respectfully requested that it be withdrawn.

CONCLUSIONS

In view of the above, Applicants submit that the pending claims are in condition for allowance on the grounds that arguments provided fully distinguish over the teaching of the art by a preponderance of the evidence. Withdrawal of the rejection is, accordingly, respectfully solicited.

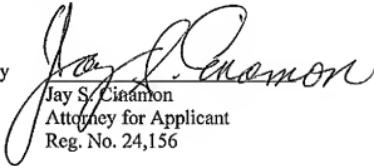
The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

ABELMAN, FRAYNE & SCHWAB
Attorneys for Applicant

By


Jay S. Cynamon
Attorney for Applicant
Reg. No. 24,156

666 Third Avenue
New York, NY 10017-5621
Tel.: (212) 949-9022
Fax: (212) 949-9190